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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,439	05/08/2002	Guy Serre	217415US0PCT	4236

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,439	SERRE ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7 and 10-22* is/are pending in the application.

4a) Of the above claim(s) *6 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5,7, 10-18 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 2/11/04, is acknowledged.

2. Claims 1, 3, 5-7 and 10-22 are pending.

3. Claims 6 and 19-21 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1, 3, 5,7, 10-18 and 22 are under consideration as they read on a citrullinated polypeptide derived from all or part of the sequence of the α-chain of a vertebrate fibrin by substitution of at least one arginine residue with a citrulline residue an antigenic composition, and a kit.

5. The notice of appeal filed on 2/11/04 appears to be inadvertent filed under 37 CFR 1.191(a). During a telephone conversation with Daniel J. Pereira, wherein Mr. Pereira indicated that the notice of Appeal was unintentionally filed in response to the non-Final Office Action mailed 8/13/03. Applicant in replying to this Office action must make affirmation of Applicant's position.

6. The following new ground of rejection is necessitated by the amendment submitted 2/11/03.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 5, 7, 10-12 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite for being in improper Markush format. Claim 1 is missing the use of the conjunction "and" after "b) a citrullinated α-chain of a mammalian fibrinogen". See MPEP 706.03(Y).

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 3, 5, 7, 10, 11-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "rheumatoid arthritis-specific autoantibodies" claimed in claim 1, line 2 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 2/11/04 points to the specification at pages 3, 6-10, 13-14 and 15-17 for support for the newly added limitations "rheumatoid arthritis-specific autoantibodies" as claimed in claim 1. However, the specification does not provide a clear support for such limitation. It is noted that the specification discloses the use of anti-filaggrin autoantibodies (AFA). Applicant has not described a genus of antibodies such as APF, AKA or other RA-specific autoantibodies. The instant claims now recite a limitation which was not clearly disclosed in the specification and recited in the claims as originally filed.

11. In view of the amendment filed on 2/11/04, only the following rejections are remained.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 3, 5,7, 10-18 and 22 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified citrullinated polypeptide of human α-chain fibrin comprising SEQ ID NO: 1 that has a molecular weight of 64-78 KDa, by substitution of at least one arginine residue with a citrulline residue which reacts with rheumatoid arthritis-specific autoantibodies, a composition and a kit thereof for the diagnosing the presence of rheumatoid arthritis does not reasonably provide **enablement** for any purified citrullinated polypeptide which reacts with rheumatoid arthritis-specific autoantibodies selected from a citrullinated α-chain of any "mammalian fibrin", "a citrullinated α-chain of a mammalian fibrinogen" or any fragment of at least 5 consecutive amino acids of a citrullinated α-chain of a mammalian fibrin and which also comprises at least one citrulline residue in claim 1, any antigenic composition for diagnosing the presence of rheumatoid arthritis-specific autoantibodies in a biological sample, comprising at least on citrullinated polypeptide optionally labeled with or conjugated to a carrier molecule in claim 5 or a pharmaceutical composition, comprising at least one citrullinated polypeptide and a carrier in claim 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 8/13/04.

The specification discloses the citrullinated human a-chain fibrin comprising SEQ ID NO:1 with the molecular weight 64-78 was identified with rheumatoid arthritis-specific autoantibodies

Applicant's arguments, filed 2/11/04, have been fully considered, but have not been found convincing.

Applicant asserts that SEQ ID NO: 1 is not the sequence of the peptide which had been tested against rheumatoid arthritis specific autoantibodies but represents the results of an amino terminal sequencing of w64-78 antigen which permitted the present inventors to identify that the antigen was, in fact, a citrullinated simple α-fibrin. Support for this is shown on page 12-13 of the application.

The Examiner Agree with the Applicant assertion, however Applicant purified only citrullinated human α-chain fibrin.

Regarding the claimed fragment of at least 5 consecutive amino acids of a citrullinated α-chain of any mammalian fibrin, Applicant submits that obtaining a fragment of more than 5 amino acids of α- fibrin that react with rheumatoid arthritis specific autoantibodies does not require undue experimentation because one can simply cut fibrin into fragments, for example, using a protease. Equally feasible is to synthesize a peptide representing known of fibrin sequences which comprise at least one arginine residue in which the peptides are subsequently citrullinated or citrullinated during synthesis. Applicant provides examples of these known sequences as entries from the PubMed database. Further, Applicant submits that based on these and other sequences it is known that human fibrin and fibrin from other vertebrates are sure of several regions of strong emology which also comprises arginine residues.

However, none of the examples provided by applicant teach a citrullinated α-chain of fibrin/fibrinogen. Therefore the examples do not address the issue at hand. Further the specification on page 9, line 36 through page 10 line 4, discloses 48 AFA-positive rheumatoid sera that were tested and show that 40 of the sera recognized W64-78 (band), 39 recognized W55-61 (band), 37 recognized both and 3 recognized only W64-78 and 2 recognized only W55-61. No fragments are disclosed to be recognized by the autoantibodies, only the full length of the human α/β fibrin are disclosed in the specification. Further, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various fragments recited in the instant claims. A person of skill in the art would not know which fragment sequences are essential, which fragment sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular fragment sequences or sequence lengths as essential for which reacts with rheumatoid arthritis-specific autoantibodies. Without detailed direction as to which fragment sequences are essential to the function of the citrullinated polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of fragments sequences encompassed by the instant claims would share the ability to react with rheumatoid arthritis-specific autoantibodies, other than the human α-chain fibrin comprising of SEQ ID NO:1.

Applicant draws the Examiner's attention to Example 2 on page 15-16 of the specification. Applicant contends that citrullination of α-fibrinogen (which has a more complex structure than

fibrin fragment and fibrin) enables it to react with RA-specific autoantibodies. However, the specification on page 13, lines 10-15 discloses that the apparent molecular weight of the w64-78 antigen is compatible with the respective theoretical molecular weight values for the α-chain of human fibrin. Further, example 2 tested only human fibrinogen as disclosed on page 15, lines 19-22 "The human fibrinogen was incubated". However what was detected is the α-chain of fibrinogen by the antibodies, which was identified to correspond to the "α-chain fibrin" as disclosed 15, lines 10-15 of the instant specification. Therefore, the specification does not provides sufficient guidance for the skilled artisan as to what fragments of the α-chain fibrinogen can be citrullinated, other than the human α-chain fibrin.

Applicant submits that partial citrullination of arginine residues resulting in a charge heterogeneity does not affect the reactivity to RA specific antibodies. Applicant directs the Examiner's attention to Example I on page 11 and Figure2 to demonstrate that the antigens w64-78 and 55-61 recognized by antifilaggrin autoantibodies (AFA) have heterogeneous pI.

The Examiner agrees with the Applicant assertion only to the extent of w64-78 and 55-61 fibrin, but not with fragments of these fibrins. As mentioned in the previous Office action, Taresa et al teaches that arginines located near the amino terminus are poorly modified, arginines in highly α-helical protein structures are only slowly modified to near completion and arginines in proteins of little structural order are rapidly modified to near completion. The PAD reaction is dependent on both substrate structure and precise sequence around the arginine residues (see page 30714 l, 2nd col., last paragraph). Thus it is unpredictable if the fragments of α-chain fibrin would be citrullinated because the PAD reaction depends on both substrate structure and precise sequence around the arginine residues.

Regarding the ability of the citrullinated polypeptides to be used as a pharmaceutical, Applicant directs the Examiner's attention to the specification on page 5 where the ability of the citrullinated polypeptides to neutralize the autoimmune response in RA-type diseases is described. Further, based on their identification and role in the autoimmune response it is reasonable that the polypeptides can be used in such a manner (see pages 1-2 of the present specification concerning the autoimmune response related to RA).

However, in view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective citrullinated α-chain fibrin-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively neutralize the autoimmune response in RA-type disease and absent working examples providing evidence which is reasonably predictive that the claimed citrullinated α-chain fibrin are effective for neutralizing the autoimmune response in RA-type diseases.

14. Claims 1, 3, 5,7, 10-18 and 22 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 8/13/04.

Applicant is in possession of a purified citrullinated polypeptide of human α-chain fibrin comprising SEQ ID NO: 1 that has a molecular weight of 64-78 KDa, by substitution of at least one arginine residue with a citrulline residue which reacts with rheumatoid arthritis-specific autoantibodies, a composition and a kit thereof for the diagnosing the presence of rheumatoid arthritis.

Applicant is not in possession of any purified citrullinated polypeptide which reacts with rheumatoid arthritis-specific autoantibodies selected from a citrullinated α-chain of any "mammalian fibrin", "a citrullinated α-chain of a mammalian fibrinogen" or any fragment of at least 5 consecutive amino acids of a citrullinated α-chain of a mammalian fibrin and which also comprises at least one citrulline residue in claim 1, any antigenic composition for diagnosing the presence of rheumatoid arthritis-specific autoantibodies in a biological sample, comprising at least on citrullinated polypeptide optionally labeled with or conjugated to a carrier molecule in claim 5 or a pharmaceutical composition, comprising at least one citrullinated polypeptide and a carrier in claim 10.

Applicant's arguments, filed 2/11/04, have been fully considered, but have not been found convincing.

Applicant argues that a relevant inquiry to written description is whether one of skill in the art would recognize that the Applicants' had possession of the claimed invention. Here, there is no question that Applicants' had possession of citrullinated polypeptides of the a chain of firbin, α chain of fibrinogen and fragments of the α-chain of fibrin that contain at least 5 consecutive amino acids and at least one citrulline residue. Applicant submits that the application describes that the citrullination of fibrin and fibrinogen sequences provides antigens that react specifically with rheumatoid arthritis autoantibodies. Further, fibrin and fibrinogen alpha chain sequences are known.

Applicant's disclosure of α-chain fibrin (MW 64-78) in the instant specification appear to be limited to human and therefore do not provide additional insight into the identification of a representative number of species to provide written support for the broadly claimed genera. The specification neither discloses any such citrullinated fragment of fibrin nor provides any suggestion as to how such fragments could be made or otherwise obtained other than by trial-and-error research. Further, the specification identifies the citrullinated w64-78 antigens to be compatible with the respective theoretical MW value of the human α-chain fibrin. Therefore, the specification does not describe a citrullinated α-chain fibrinogen that is immunoreactive with AFA autoantibodies.

15. The certified English translation of the France Patent application 99/08470, filed 07/01/1999, is sufficient to overcome the rejection of claims 1-3, 5 and 10 under 35 U.S.C. 102(a) as being anticipated by Masson-Bessiere et al (Rev. Rheum., December 1999, 66:754).

16. The certified English translation of the France Patent application 99/08470, filed 07/01/1999, is sufficient to overcome the rejection of claim 5 under 35 U.S.C. 103(a) as being unpatentable over Masson-Bessiere *et al* in view of U.S. Patent No. 5,858,723.

17. The certified English translation of the France Patent application 99/08470, filed 07/01/1999, is sufficient to overcome the rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over Masson-Bessiere *et al* in view of U.S. Patent No. 4,281,061.

18. In view of Applicant's convincing argument, the previous rejection of claims 1-3 and 10 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,821,068 in view of Schellekens et al is hereby withdrawn.

19. In view of Applicant's convincing argument, the previous rejection of claim 5 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,821,068 in view of Schellekens et al as applied to claims 1-3 and 10 above, and further in view of U.S. Patent No. 5,858,723, is hereby withdrawn.

20. In view of Applicant's convincing argument, the previous rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,821,068 in view of Schellekens *et al* as applied to claims 1-3, 5 and 10 above, and further in view of U.S. Patent No. 4,281,061, is hereby withdrawn.

21. No claim is allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
April 16, 2004

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